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Joseph R. Baker, APC
Gavrilovich, Dodd & Lindsey LLP
4660 La Jolla Village Drive, Suite 750
San Diego, CA 92122

EXAMINER	
POPA, ILEANA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/045,178	KASAHARA ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *41, 43-46, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,43-45,49-51,56,58,59,61,63-73,75,78-82 and 87-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/28/2009 has been entered.

Claims 1-40, 42, 47, 48, 52-55, 57, 60, 62, 74, 76, 77 and 83-86 have been cancelled. Claims 41, 66, 80, 81, 82, 87, 89, 91, 93, 95, 97, 100, 102-105, 107, 109, 111, 113, 119 and 121 have been amended. Claim 46 has been withdrawn.

Claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 are under examination.

2. The objection to the specification is withdrawn in response to Applicant's amendments filed on 05/26/2009.

The provisional rejection of claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 remain on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 23, and 26-34 of copending Application No. 11/805,411 in view of both Yan et al. (Prostrate, 1997, 32: 129-139, of record) and Sobol et al. (U.S. patent No. 5,674,486) is moot because Application No. 11/805,411 has been abandoned.

The rejection of claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, 87-121 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendments filed on 09/28/2009.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. (Cancer Research, 1993, 53: 83-88), in view of each Martuza et al. (U.S. Patent No. 5,585,096), Murakami et al. (Gene, 1997, 202: 23-29), and Sobol et al. (U.S. patent No. 5,674,486).

Claims 49-51, 70, 80, 91, 102, 109 and 115 recite GAG, POL and ENV from MLV and not MoMLV. However, MLV is not a species but rather a genus comprising several species of murine leukemia viruses among which is Moloney murine leukemia virus (MoMLV). Because the claims do not specifically recite an MLV species and because the only MLV species envisioned by the instant specification is MoMLV, claims 49-51, 70, 80, 91, 102, 109 and 115 are interpreted as being drawn to MoMLV.

Ram et al. teach a method of treating glioblastoma (i.e., a cell proliferative disorder) in rats by the *in vivo* intratumoral administration of a therapeutically effective amount of cells producing a retrovirus comprising 5' and 3' long terminal repeats (LTR) and a heterologous nucleic acid sequence encoding the HSV thymidine kinase (tk) (i.e., a suicide gene) that uses the 5' LTR as its promoter (i.e., operably linked to a regulatory nucleic acid sequence), followed by contacting the rats with ganciclovir (i.e., a prodrug), wherein the ganciclovir is activated by the tk expression; since the cells are administered to the animal, they must necessarily be administered in a pharmaceutically acceptable carrier (i.e., the retrovirus is contained in a pharmaceutically acceptable carrier) (claims 41, 44, 45, 66, 78, 79, 87, 89, 97, 100, 105, 107, 119, and 121) (Abstract, p. 83, columns 1 and 2, p. 84, column 1, p. 85, column 2). Ram et al. teach that the retroviral vector is MoMLV, i.e., a mammalian oncoretrovirus (claims 49, 61, 70, 80, 91, 99, 102, 109, and 115) (p. 83, column 1). Ram et al. teach their approach as suitable for the treatment of localized tumors in humans (Abstract, p. 83, column 2, second full paragraph, p. 88, column 1).

Ram et al. teach administering cells producing replication deficient MoMLV and not a replication competent retrovirus, as recited by the instant claims 41, 66, 80, 87, 89, 91, 97, 100, 102, 105, 107, 109, 119, and 121. However, at the time of filing, the advantages of using replication competent retroviruses for cancer treatment was taught by the prior art. For example, Martuza et al. teach that the administration of replication deficient viruses or of cells producing replication deficient viruses is not applicable to the treatment of tumors in humans because, since the virus cannot replicate, gene transfer

occurs within a few cell-distances, which leads to inefficient gene delivery; for these reasons, Martuza et al. suggest the use of replication competent viral vectors (including retroviral vectors) (column 2, lines 1-45, column 5, lines 14-18). Martuza et al. teach that such replication competent viruses can be used to treat melanoma (claims 56, 75, 98, and 101) (column 3, lines 52-55). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. by using a replication competent MoMLV (i.e., an oncoretrovirus comprising MoMLV GAG, POL, ENV, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration into a target cell), with a reasonable expectation of success. The motivation to do so is provided by Martuza et al., who teach the necessity to replace replication deficient viruses with replication competent viruses for efficient gene therapy in animals and humans. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that replication competent viruses can be successfully obtained and used for cancer treatment. With respect to the limitation of the MoMLV being an amphotropic MoMLV (claims 50 and 71), since the teachings of Ram et al. and Martuza et al. (U.S. Patent No. 5,585,096) disclose MoMLV suitable for therapy in humans, their MoMLV must necessarily be amphotropic (i.e., allows transduction of cells of other species than the mouse).

Ram et al. and Martuza et al. do not teach a cassette comprising an internal ribosome entry site (IRES) operably linked to the suicide gene, wherein the cassette is located 5' to the 3' LTR and 3' to the sequence encoding ENV (claims 41, 66, 80, 87,

89, 91, 97, 100, 102, 105, 107, 109, 119, and 121). However, at the time of filing the use of cassettes comprising IRES operably linked to heterologous genes was known in the prior art, for example Murakami et al. teach insertions of such cassettes into retroviral vectors, wherein the cassettes are inserted 5' to the 3' LTR and 3' to the sequence encoding ENV (p. 25, Fig. 1A). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. and Martuza et al. by inserting an IRES-suicide gene cassette in their MoMLV, as taught by Murakami et al., with a reasonable expectation of success. The motivation to do so is provided by Murakami et al. who teach that introduction of such IRES cassettes 5' to the 3' LTR and 3' to the sequence encoding ENV results in increased expression of heterologous genes as compared to the vectors lacking the IRES cassettes (Abstract, p. 23, column 2, last paragraph, p. 28, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murakami et al. teach that IRES cassettes can be successfully inserted into retroviral vectors.

With respect to the limitation of a viral vector encoding a cytokine (claims 97, 100, 102, 105, 107, 109, and 119), Martuza et al. teach tumor killing by using replication competent viruses lacking a suicide gene and comprising a gene encoding a cytokine, wherein tumor killing is enhanced by cytokine expression in the tumor (column 11, lines 35-55). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made to substitute the suicide gene with a gene encoding a cytokine to achieve the predictable result of killing tumor cells. With respect to the limitations

recited in claims 116-118, it is noted that the art teaches cancer therapy by using a variety of cytokine, including IFNγ (see Sobol, Abstract, column 4, lines 25-27). It would have been obvious to one of skill in the art, at the time the invention was made to use a gene encoding IFNγ to achieve the predictable result of treating cancer.

With respect to the limitation of treatment by using a recombinant replication competent oncoretrovirus (instant claims 41, 80, 81, 87, 91, 93, 97, 102, 103, 105, 109, and 119), it is noted that the administration of the replication competent MoMLV to a patient would necessarily result in the *in vivo* production of the virus, and therefore, the combined teachings above embrace a method of treatment by using a recombinant replication competent MoMLV.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

5. Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of Douar et al. (Gene Ther, 1996, 3: 789-796, Abstract).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach a non-retroviral envelope, such as that of VSV (claims 119 and 120). Douar et al. teach VSV-G pseudotyped MoMLV (Abstract). It would have

been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by using a VSV-G pseudotyped MoMLV, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Douar et al. teach that VSV-G pseudotyped MoMLV has a broader host range. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that VSV-G pseudotyped MoMLV can be successfully obtained and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

6. Claims 41, 43-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 78-80, 87-92, 97-102, 105-110, 115-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Vile et al. (Virology, 1995, 214: 307-313) and Yan et al. (Prostrate, 1997, 32: 129-139).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 106, 108, and 110). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column

1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Vile et al. do not teach the probasin promoter (claim 59). However, at the time of filing the probasin promoter was known and used in the prior art, for example the probasin promoter was used by Yan et al. to target gene expression in the prostrate (Abstract, p. 130, columns 1 and 2, p. 133, column 2). Therefore, one of skill in the art would have known to use the probasin promoter to specifically target the suicide genes to prostrate tumors for increased treatment efficiency of such tumors.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 41, 43-45, 49-51, 56, 58, 61, 63-73, 75, 78-82, 87-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Kasahara et al. (Science, 1994, 266: 1373-1376) and Vile et al.

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza, Martuza et al., Murakami et al., and Sobol et al. do not teach a chimeric envelope, wherein the chimeric protein comprises a targeting ligand such as a receptor ligand (claims 63-65, 67-69, 73, 81, 82, 93, 95, 103, 104, 111, and 113) or an ecotropic envelope (claim 72). Kasahara et al. teach tissue specific targeting of MoMLV retroviral vectors to cells expressing the erythropoietin (EPO) receptor by engineering the vector to encode a chimeric ecotropic MoMLV protein, wherein the chimeric envelope protein comprises EPO (p. 1373, column 2, p. 1374, column 3 bridging p.1375). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by engineering their vector to encode an ecotropic envelope fused to a receptor ligand, with a reasonable expectation of success. The motivation to do so is provided by Kasahara et al., who teach that such viruses can be used to specifically infect human cells expressing the receptor for the ligand and that such a strategy can be used for the treatment of cancer (p. 1373, column 1, p. 1375, column 1 bridging column 2, and column 3). One of skill in the art would have been expected to have a reasonable

expectation of success in doing such because the art teaches that such engineered retroviruses can be successfully made and used.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 94, 96, 106, 108, 110, 112, and 114). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al., by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicants traversed all rejections above for the reasons previously set forth in the Response filed August 2008. Furthermore, Applicants provide the following additional remarks, information and evidence (Exhibit B).

Ram et al. provides replication defective retroviral vectors that require a helper cell line for replication. Martuza et al. provides a DNA viral vector derived from Herpes Simplex Virus, a complex lytic DNA virus that induces cytotoxicity. Murakami et al. provides recombinant Rous Sarcoma Virus that cannot infect mammalian cells and which comprises a disposable gene thus provided a flexible naturally inherent cassette.

Applicant submits that one of skill in the art would not be motivated to generate Applicant's claimed invention from any combination of the foregoing references. It is important to understand that the uses, genomes and ability to infect mammalian cells are drastically different in each of the vector systems described in these references. It is not a matter of piecing together the various references as suggested by the Office Action. For example, truly piecing the references together would require placing a DNA genome in an RNA vector that can only infect avian cells and somehow making it infect mammalian cells without losing stability. As described in the prior response, one of skill in the art would not mix and match the genomes of the various vectors as suggested by the Office Action.

For example, Exhibit A (Oh, et al., J. of Virol., 76(4):1762-1768, 2002) demonstrates that even after the priority date of the present invention, those of skill in the art would not have been motivated to generate vectors as set forth by the present

claims by mixing/matching RSV and oncoretroviruses. For example, paragraph 2, column 1 at page 1762 of Oh et al., states:

> Most retroviral genomes cannot accommodate the insertion of significant amounts of additional genetic information. In these cases, viral sequences must be removed to provide a place for whatever additional information is inserted. Such viruses are, by definition, replication defective. The missing viral genetic information must be supplied in trans, either by a helper cell or a helper virus. There is one exception. Avian leukosis viruses can accept approximately 2.5 kb of additional information: the naturally occurring avian leukosis virus derivative Rous sarcoma virus (RSV) contains, in addition to a full complement of viral genes, the src oncogene (21).

Simply put, the foregoing paragraph actually teaches away from the use of mammalian oncoretroviral vectors because they must be rendered "defective" to accommodate additional genetic material, unless one uses the "one exception" an RSV vector which includes the dispensible src gene. This statement and the cited reference are consistent with the remarks Applicant provided in the prior response - simply that one of skill in the art would not modify the teachings of Murakami et al. (regarding RSV viral vectors) to non-RSV vector systems due to the inability of such mammalian retroviral systems to accommodate additional genetic sequences.

The present application describes compositions and methods whereby this "inability" is overcome. Such an advance in the art is one of the main purposes and policies behind the patent system, i.e., to protect advances in the art and give to the inventors a limited time of exclusivity for their hard work and development.

With respect to Martuza et al., one of skill in the art would recognize that the genome of Herpes virus has little if any similarity in its genome, infectivity or life cycle to oncoretroviral vectors such as MLV. For example, Herpes virus is a lytic virus having cellular toxicity. In addition, herpes virus is far more complex and is a DNA virus. One

of skill in the art would not translate the teachings in the Herpes viral arts to those of the oncoretroviral arts due to such drastic differences in genomes, infectivity and viral life cycle.

Thus, the three references of Ram et al., Martuza et al., and Murakami et al. cannot be combined without substantial changes to the genomes of the vectors described and modifications of the references that are not suggested by the art. In other words, one of skill in the art would have to discard the teachings of the references themselves to arrive at Applicant's claimed invention.

For example, in order to utilize Sobol et al. as suggested by the Office Action, one of skill in the art would have to discard the teaching in the reference that replication competent vectors should be discarded as being dangerous. As another example, one of skill in the art would have to discard the teachings of Oh et al. and others in the art that oncoretroviral vectors cannot be modified to incorporate additional sequences even though Oh et al. says RSV is the "one exception".

Applicant through extensive experimentation and development demonstrates that not just any combination of elements (as suggested by the Office Action), not just any insertion site (as suggested by the Office Action) and not just any viral vector (as suggested by the Office Action) would result in Applicant's claimed invention. Applicant was the first to discover that the combination of virus selection and IRES cassette insertion site provides a competent, stable and effective RCR system for treating cell proliferative disorders.

For example, Logg et al., J. of Virol., 75(15):6989-6998, 2001 sets forth the importance of the cassette location. The combination of transduction efficiency, transgene stability and target selectivity was unknown in any recombinant replication competent mammalian oncoretrovirus prior the instant vector. The methods (and the vector composition used in the methods) provides insert stability and maintains transcription activity of the transgene and the translational viability of the encoded polypeptide.

Applicant submits that the high-level view taken by the Office (1) fails to consider the modifications that must be made to each reference to arrive at the invention that go far beyond mere routine experimentation and (2) disregard accepted principles at the time the invention was made that replication competent retroviral vectors were unacceptable, that RSV was an "exception" to the viral vector limitations, and that HSV are not lytic and can be modified for the same purpose as the present invention. Applicant submits that the foregoing (i) lack of motivation, (ii) modifications to the references required to make them even remotely functional, and (iii) general disregard for accept principles at the time of the invention, cannot be merely discarded by a general assertion to the skill in the art.

Applicant argues that the references either individually or in combination do not provide the necessary factors to set forth a prima facie case of obviousness.

As the Examiner indicates Ram et al. fail to teach or suggest a recombinant replication competent oncoretroviral vector or recombinant plasmid or recombinant polynucleotide encoding a replication competent oncoretroviral vector. Furthermore,

Ram et al. fail to teach or suggest treating a tumor in the absence of a helper cell to assist in the defective viral replication, Ram et al. fail to teach or suggest a cytokine transgene, Ram et al. fail to teach or suggest a chimeric env protein, Ram et al. fail to teach or suggest a tissue specific promoter, and Ram et al. fail to teach or suggest an IRES cassette. Ram et al. is far removed from the methods and compositions of Applicant's invention, which utilize a replication competent, non-helper cell system to treat a cell proliferative disease or disorder. Ram et al. describe a method that utilizes "retroviral producer cells" injected at the site of a tumor (see page 86, column 2, last paragraph of the cited reference). The producer cells support the in situ production of a retroviral vector containing a suicide gene. The producer cells are necessary because the vector is not replication competent. Further, the nucleic acid sequence encoding the suicide gene is located "just downstream of the 5' long terminal repeat sequence" (see page 84, column 1, lines 2-4 of the cited reference) in a location different from Applicant's claimed vector. It is clear from the contents of the cited reference that Ram et al. fail to appreciate the significance of utilizing a replication competent oncoretrovirus in the absence of a producer cell to achieve efficient transduction. Because Ram et al. use a gutted vector in order to incorporate the transgenes (see, Oh et al. described above), transcription of a transgene can easily be effected off the regulatory region of the 5'LTR. In contrast, Applicant's transgene is not directly linked to the 5'LTR. The location of the transgene and the IRES as set forth in Applicants' claims is not an insignificant modification. Thus, Ram et al. is deficient in at least three aspects: (1) the vector is replication defective; (2) the methods require a help cell; and (3) the transgene

location is of little or no important to Ram et al. The gutted size and location of the transgene in Ram et al. allow for the 5' LTR to serve as the regulatory region.

To overcome these deficiencies the Office combines Ram et al. with Martuza et al. Martuza et al. allegedly teaches replication competent viral vectors derived from adenovirus and herpes simplex virus (such vectors are DNA vectors - very different than RNA vectors). Applicant submits this is the first of many leaps the Office makes to overcome voids in the development of Applicant's claimed invention. First, it is not clear why one would combine a defective retrovirus of Ram et al. with a DNA virus of Martuza et al., the genomes are completely different. Nevertheless, when the references are combined the combination still fails to teach or suggest Applicant's claimed invention. Like Ram et al., Martuza et al. fail to appreciate the importance of positioning a heterologous sequence encoding a therapeutic polypeptide in a region outside the LTR or not linked directly to the LTR of the viral vector. Nor does the combination of references teach, suggest, or appreciate an internal ribosome entry site. As will be recognized by the Examiner and those of skill in the art, merely inserting a transgene into a replication competent retrovirus does not provide a reasonable expectation that infectivity, stability or continued transmission and expression of the transgene will occur. In fact, numerous peer-reviewed journal articles indicate that insertion of transgene into U3 and other locations within a replication competent retrovirus can cause a loss of replication, and genetic instability of the vector (see, e.g., Logg et al. supra). Thus, the combination of Ram et al. and Martuza et al. fail to teach or suggest Applicant's claimed

invention and do not provide any reasonable expectation of success in achieving a RCR having the transmission and genetic stability of Applicant's claimed vectors.

To overcome the deficiencies of Ram et al. and Martuza et al., the Office combines Murakami et al. Murakami et al. use a Rous Sarcoma Virus. As stated by Oh et al. (Exhibit A), the RSV is the one "exception" to retroviruses. The IRES-transgene insertions described in Murakami et al. consist of an IRES-transgene sequence positioned 3' to the env-encoding sequence and 5' to the 3' LTR. However, the cited reference utilizes replication competent avian sarcoma viruses (RCAS) which are distinct from the oncoretroviruses of the pending claims and incapable of replication in mammalian cells. Thus, the RSV vector could not be used to treat a mammal as set forth in Applicant's claims. The inability of RSV to produce infective viral particles in mammalian cells is disclosed in several peer-reviewed journal articles. Here, again, the Office makes a leap from a defective gutted retroviruses, to DNA viruses to avian viruses, with little direction, suggestion or likelihood of success in the art particularly when the RSV virus is recognized as an exception for its ability to incorporate transgenes into its genome. It is only through Applicant's disclosure and hindsight reconstruction that such very different viral architectures and functions can be pieced together. For example, Avian Rous Sarcoma Virus naturally carries extra sequences (the src oncogene, which is in addition to the gag, pol and env genes required for replication, and which is similar in size to the env gene) positioned just after env. Thus, RSV evolved a capacity to incorporate a large piece of extra sequence in this location in its genome, something not found in mammalian oncoretroviruses. The idea of putting

an IRES-transgene insert after the env gene in a mammalian oncoretrovirus would not be obvious in view of the cited references simply because there are no known naturally-evolved replication-competent mammalian oncoretroviruses with extra genes following the env (or anywhere else, for that matter). In fact, it was recognized in the art that inserting a transgene in the region following the env gene although providing short term expression ultimately resulted in genetic instability and loss of the transgene in subsequent rounds of replication. RSV through natural development has developed a "transgene insertion site" because it contained a non-essential and replaceable gene (src), thus providing additional flexibility (i.e., an "exception") compared to mammalian oncoretroviruses.

Further, combining the IRES-transgene of Murakami et al. and the vector described by Martuza et al. would not result in a vector or method described or claimed in the instant application. It is not clear why or how one would combine a DNA viral vector and an RNA avian viral vector.

Finally, the Office combines Sobol et al. with Ram et al., Martuza et al., and Murakami et al., for the teaching of cytokines to treat cancer. The Office appears to be picking and choosing the use of certain reference and avoiding the teachings of the reference as a whole. When taken as a whole, Sobol et al. actually teach that one should avoid the use of replication competent retroviruses. For examples, Sobol et al. teach throughout the specification that one should use proper screening, production and removal of replication competent retroviruses from any system or method. However, even in view of such a teaching away, Sobol et al. do not remedy the deficiencies as set

forth above regarding the replication competent retrovirus and use of such recombinant viral vectors for the treatment of cell proliferative disorder.

Not only do the cited references when combined fail to identify predictable solutions for achieving a replication competent oncoretrovirus capable of delivering a therapeutic polypeptide to dividing cells, they also fail to provide all the components necessary for the production of the vector set forth in the claimed methods.

In contrast, the Applicant has succeeded in developing a replication competent oncoretroviral vector with an enhanced capability to stably deliver a heterologous sequence to a dividing mammalian cell. Once integrated into a target cell, the novel vector produces a therapeutic polypeptide encoded by the heterologous sequence. In addition, viral particles which infect neighboring dividing cells are also produced in the absence of helper cells.

It is important to understand that the surprising combination of transduction efficiency, transgene stability, and target selectivity provided by Applicant's invention were simply unknown in any recombinant replication competent mammalian oncoretrovirus prior to the Applicant's invention. When placed in a mammalian oncoretroviral background, the cassette is useful for the stable expression of a transgene coding sequences including marker genes such as green fluorescent protein (GFP), suicide genes such as thymidine kinase, cytosine deaminase (CD) or purine nucleoside phosphorylase (PNP), and genes encoding cytokines such as interferon. For at least the foregoing reasons, the pending claims are novel and non-obvious over the cited reference. Accordingly, Applicants request the withdrawal of this rejection.

Applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

The majority of Applicant's arguments are not new and were previously addressed. The new arguments are answered below.

Applicant argues that Oh et al. (Exhibit A) teach away from the use of replication competent mammalian oncoretroviral vectors because, in order to accommodate additional genetic material, they must be rendered defective. This argument is not found persuasive. Using replication competent retroviral vectors (including MLV) with foreign genes and IRES introduced into their genome was routine in the prior art. Furthermore, using replication competent MLV vectors with IRES-transgenes cassettes introduced 3' to ENV was taught by the prior art (see Stull et al., U.S. Patent No. 6,322,969, of record, Fig. 2 and 4, column 14, lines 25-41, column 24, lines 15-27). Therefore, the instant invention is not the first to describe such vectors. At the time the invention was made, one of skill in the art would have known that the teachings of Murakami et al. can be extrapolated to MLV.

Applicant argues that Sobol et al. teach that replication competent vectors should be discarded as being dangerous. This is not found persuasive because: **(i)** the prior art recognizes the necessity of replacing replication deficient oncoviral (including MLV) vectors with replication competent vectors for gene therapy (see the teachings of Martuza et al. above; Stuhlmann et al., Mol. Cell. Biol., 1989, 9: 100-108, Abstract, p. 100, column 1, p. 107, column 2, last paragraph) and **(ii)** Sobol et al. teach that replication competent retroviruses MLV are not harmful for humans (column 5, lines 23-

31). Based on these teachings, one of skill in the art would have known that replication competent MLV is suitable for therapy in humans.

Applicant argues that the instant invention demonstrates that not just any combination of elements (as suggested by the Examiner), not just any insertion site (as suggested by the Examiner) and not just any viral vector (as suggested by the Examiner) would result in Applicant's invention. This is not found persuasive. The Examiner did not combine any but rather specific elements, a specific insertion site, and a specific vector (see the rejection above). That replication competent MLV (i.e., having Gag, Pol and Env) was suitable for gene therapy was known in the prior art. Similarly, the advantages of inserting the IRES cassette 3' to the Env (i.e., increased stability, higher transgene expression levels and increased biological effects *in vivo*) was taught by the prior art (see Murakami et al., Abstract, p. 27, column 2, p. 28, columns 1 and 2). For the same reasons, Applicant's argument that he was the first to discover that inserting IRES 3' to the Env provides insert stability and maintains transgene expression is not found persuasive.

For the reasons set forth above, the opinion provided by Dr. Chiang in Exhibit B is not found persuasive (it is noted that Exhibit B presents the same arguments as above). Apart from an opinion that replication competent retroviral vectors in general are not suitable for therapy, Exhibit B does not provide any evidence demonstrating that, at the time the instant invention was made, the art was moving away from using replication competent MLV vectors in gene therapy. The instant rejection is not drawn

to just any retrovirus but rather to MLV. The prior art teaches the necessity to use replication competent viruses in cancer therapy and that MLV is not harmful for humans.

8. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ileana Popa/

Primary Examiner, Art Unit 1633